Auditory perception and language comprehension in aphasia – An event-related brain potentials (ERP) study

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Introduction

Aphasia

Aphasia can be defined as an impairment of normally developed language ability due to brain injury (Reinvang 1985a). The most common etiologies are stroke (foremost cerebral infarctions, but also hemorrhages), traumatic brain injuries, brain tumors and infections of the brain. The brain lesion is usually located in an area which receives its blood-supply from the left medial cerebral artery, namely in the left hemisphere in frontal, temporal or parietal regions around the Sylvian fissure.

There are no epidemiological studies on the incidence or prevalence of aphasia in Norway, but estimations can be made from numbers on stroke and on the frequency of aphasia in stroke. The stroke-incidence in Norway is between 14.000 and 15.000 (Ellekjaer, Holmen, Indredavik & Terent 1997). Based on results from international studies finding aphasic symptoms in 20 % (Wade, Hewer, David & Enderby 1986) to 38 % (Pedersen, Jorgensen, Nakayama, Raaschou & Olsen 1995) of all acute stroke patients and on a Norwegian population of 4.681.400 (Statistics Norway 2006), it can be assumed that between 2.800 and 5.700 Norwegians become aphasic due to stroke every year.

The prevalence of stroke in Norway has been estimated to slightly exceed 50.000 (Wyller 1998). Studies from other countries suggest that about one fifth of all stroke patients remain aphasic in chronic stages (e.g. Pedersen et al. 1995 (18 %), Kauhanen et al. 2000 (23 %)). This corresponds to a Norwegian aphasia prevalence of approximately 10.000 due to stroke only. Sundet and Reinvang give a “cautious estimate” of aphasia prevalence in Norway of about 5.000 subjects due to stroke (Sundet & Reinvang 1988), but on the basis on the newer numbers of stroke incidence and prevalence in Norway (see above), this estimate seems too low. Numbers on aphasia incidence and prevalence due to other reasons than stroke are not available and estimations are difficult to make.

Aphasia usually affects both the ability to produce and to understand speech, although impairments of production in many cases are graver than comprehension difficulties. Usually several linguistic levels are compromised, i.e. difficulties in the correct use of speech with regard to phonological, morphological, syntactical, and semantical functions can occur. While aphasia can appear without the presence of other cognitive impairments, it often occurs in coincidence especially with apraxia, memory disorders or attention disorders.

Several theoretical fundaments for aphasia research and treatment exist. According to Basso (2003), the most influential concepts are associationism (e.g. Broca 1861; Wernicke 1874), holism (e.g. Goldstein 1948; Hughlings-Jackson 1878), neoassociationism (e.g. Geschwind 1965) and – as an intermediate position between associationism and holism – functionalism (e.g. Luria 1970). In the recent decades, the most renowned and most used theoretical model of aphasia – at least in the western world – is the so-called Wernicke-Geschwind model, an associationist, neuropsychological model that is based on the relation between different aphasia syndromes and different lesion localizations (e.g. Benson & Ardila 1996). Central in this model is the notion of separate language areas in the brain for language production (anterior language areas including the classical location of Broca's area) and for language comprehension (posterior language areas including Wernicke's area) which are interconnected. As a consequence, lesions to Broca's area usually entail language production deficits while lesions to the posterior areas have language comprehension impairments as a leading symptom. Eight main aphasia types exist according to this model which in a simplified approach also can be described by different combinations of the three parameters fluency, comprehension, and repetition (Goodglass & Kaplan 1983; cf. table 1).

Table 1. Main aphasia types and their features with regard to comprehension, fluency and repetition (according to Goodglass & Kaplan 1983)

Aphasia type	Comprehension	Fluency	Repetition
Broca's	good	non-fluent	poor
Transcortical motor	good	non-fluent	good
Conduction	good	fluent	poor
Anomic	good	fluent	good
Wernicke's	poor	fluent	poor
Transcortical sensory	poor	fluent	good
Global	poor	non-fluent	poor
Mixed transcortical	poor	non-fluent	good

Through the years however, a number of cases have been presented where the relation between lesion localization and language impairment deviates from what the original Wernicke-Geschwind model predicts (e.g. Miceli, Gainotti, Caltagirone & Masullo 1980).

Also, inter-individual differences in structural and functional language organization have been suggested with the possible consequence that the same lesion localization has different impacts in different individuals (Knecht et al. 2002). A modified model with less emphasis on the "computational" aspects of the original approach has been suggested (Goodglass 1993).

Recent research, in particular using modern neuroimaging techniques, has allowed to draw a more complex picture, although still incomplete, of how language works in the human brain and has produced evidence that large areas of the left hemisphere – and even right-hemisphere areas – are involved in language processing (for a recent review, see Demonet, Thierry & Cardebat 2005). In summary, one may conclude at this stage that it is still reasonable to hold the view that different brain areas are specialized for subfunctions involved in language processing, but that they are not activated in an automatic, step-by-step manner, but rather are involved in complex and dynamic networks that process both sequentially and in parallel involving forward and backward loops, with possible individual differences (see also below).

Regarding prognosis, a large number of aphasic patients improve, but many of them remain chronically impaired (see above). Improvement seems to be independent of sex, age or aphasia type; it can occur in relation to all linguistic levels and seems in general to be of about the same extent for comprehension, naming, and word production (Pedersen, Vinter & Olsen 2004). While large individual differences occur, the main prognostic factor in aphasia seems to be initial severity of both aphasia and the brain injury in general (Pedersen et al. 2004). The largest improvements usually occur during the first three months post injury (e.g. Laska, Hellblom, Murray, Kahan & Von 2001; Reinvang 1985a), but recent studies have shown improvement due to therapeutic interventions even in chronic stages (e.g. Pulvermüller et al. 2001).

Besides treatment of the brain dysfunction causing aphasia, the main approach in treating acquired language impairment specifically is speech and language therapy. While some authors claim that there is sufficient evidence that speech and language therapy is effective (Robey 1994), others consider the evidence as pending, at least regarding randomized controlled trials (Greener, Enderby & Whurr 2000). Different strategies of treatment exist which reflect the abovementioned theoretical approaches to aphasia: These main therapeutic approaches can be described as behavioral, functional, neurolinguistic, and pragmatic (for an overview, see Basso 2003). While the former approaches focus on the treatment of more or less specific deficits, the pragmatic approach has as its main goal to restore

communicative competence in general. It has been suggested that aphasic patients with severe language impairment should be treated with a pragmatic approach, while the therapy for mild and moderate deficits should be directed at underlying cognitive / linguistic impairments (Basso 2003). Rich stimulation with linguistic input is widely regarded as important for recovery from aphasia. Treatment intensity seems to be important for the effect of aphasia therapy (Bhogal, Teasell & Speechley 2003). With regard to pharmacotherapy of aphasia, several drugs have been suggested to ease aphasic symptoms, especially anomia, but more research is needed; based on the evidence available per date, pharmacotherapy is somewhat promising, but can not be recommended as routine therapy (Greener, Enderby & Whurr 2001; Klein & Albert 2004).

Assessment of language comprehension in aphasia

Although, as mentioned above, not all therapeutic approaches to aphasia primarily emphasize the treatment of specific impairments, assessment of the individual aphasic patient's language deficits is essential. While speech production obviously is rather easy to assess, detailed evaluation of comprehension ability can be difficult because it has to be deducted from responses made by the patient. This can be complicated by constraints to the patient's ability to respond correctly, due to for example severe speech production deficits, apraxia, visual impairments, locked-in syndrome or severe brain injury leading to tetraplegia. In addition, preserved capacity might go undetected because the patient does not understand the instruction on how to respond. Due to these reasons, clinical assessment of language comprehension functioning might be difficult, unreliable or even impossible. A method that directly registers brain activity related to language processing would therefore represent a number of advantages compared to classic clinical aphasia assessment, potentially allowing more tailored interventions in the individual patient with regard to the rehabilitation program in general as well as the aphasia treatment in particular.

Event-related brain potentials

Event-related brain potentials (ERPs) are one of several methods to study brain activity. This method based on electroencephalography (EEG) measures brain activity in correlation to stimuli presented to the investigated subject. Different waveforms, elicited by different stimuli and in different conditions or tasks, can be identified and related to sensory and cognitive processes. ERPs are especially valuable in the study of timing of cognitive processes, but to a certain degree also their location. With regard to language function, a

special advantage of ERPs is that they allow the investigation of language comprehension which is difficult to study by other means (Hagoort & Kutas 1995; Osterhout & Holcomb 1995).

A frequently used method in ERP research is the so-called oddball paradigm in which an infrequent deviant or target stimulus is presented amongst frequent standard stimuli. The investigated subject can either be instructed not to attend to the stimuli (but e.g. rather leaf through an illustrated magazine) or to detect the target stimulus and react upon it. When speech sound processing is investigated in this manner, ERP waveforms are obtained that can be related to separate processing stages: The N1 component is a negative waveform registered about 100 ms after stimulus onset elicited both by standard and target stimuli in an oddball paradigm (Näätänen & Winkler 1999; Roberts, Ferrari, Stufflebeam & Poeppel 2000). This component reflects primary auditory feature analysis and integration, which is an intermediate, preconscious stage in speech sound processing (Näätänen & Winkler 1999). N1 can be registered regardless whether the subject attends to the stimuli or not, but is found with larger amplitudes in attended conditions and with longer inter-stimulus intervals. The subsequent N2 component, which is elicited by deviant stimuli, reflects stimulus discrimination and classification processes and can be divided into (at least) three subcomponents labeled N2a, N2b, and N2c (Näätänen & Picton 1986; Pritchard, Shappell & Brandt 1991). N2a is also found in unattended stimulation paradigms, then usually called mismatch negativity (MMN; Alho 1995; Kujala, Tervaniemi & Schroger 2007; Näätänen, Gaillard & Mäntysalo 1978; Näätänen, Paavilainen, Rinne & Alho 2007; Näätänen & Winkler 1999). MMN thus reflects unattended, preconscious stimulus discrimination processes and is usually found 120 to 200 ms after the onset of stimulus change. When elicited by phonetic changes, MMN is predominant over the left hemisphere (Näätänen et al. 1997; Shtyrov, Kujala, Lyytinen, Kujala, Ilmoniemi & Näätänen 2000; Shtyrov, Kujala, Palva, Ilmoniemi & Näätänen 2000). There has been some debate on whether N1 and MMN actually reflect activity of different neural structures or not (Jaaskelainen et al. 2004; Näätänen, Jacobsen & Winkler 2005). N2b and N2c reflect processes connected to the attended discrimination of stimuli and their classification with regard to the task (Näätänen & Picton 1986; Pritchard et al. 1991). The subsequent positive deflection P3 (or P300) usually peaks between 350 and 500 ms at parietal sites (Linden 2005; Picton 1992; Polich 2007). Target detection processes as well as the initiation of a target reaction are reflected by this component.

Although the first electrophysiological investigation of aphasia was performed over 40 years ago (Liberson 1966), this line of research has grown especially during the last fifteen years. To date, quite a number of ERP studies of aphasia have been performed although they have been motivated by rather diverging research interests: A high proportion of ERP studies investigating aphasia has focused upon auditory processing and speech sound processing in aphasia (e.g. Aaltonen, Tuomainen, Laine & Niemi 1993; Csepe, Osman-Sagi, Molnar & Gosy 2001; Greenberg & Metting 1974; Ilvonen et al. 2004; Pettigrew, Murdoch, Kei, Ponton, Alku & Chenerey 2005; Strauss Hough, Downs, Cranford & Givens 2003). To a lesser degree, also disturbances in other linguistic faculties have been investigated as for example lexical-semantic processing (e.g. Hagoort 1993; ter Keurs M., Brown & Hagoort 2002) or syntactic processing (e.g. Friederici, Hahne & von Cramon 1998; Kotz, Frisch, von Cramon & Friederici 2003). Another area of research has focused on the investigation of distinct brain areas and their role in auditory and language processing (e.g. Alho, Woods, Algazi, Knight & Näätänen 1994; Knight, Hillyard, Woods & Neville 1980; Knight, Scabini, Woods & Clayworth 1989; Pool, Finitzo, Hong, Rogers & Pickett 1989). Additionally, some other research interests have been pursued, such as the study of plasticity (e.g. Hagoort, Wassenaar & Brown 2003; Ilvonen et al. 2003; Papanicolaou, Moore, Deutsch, Levin & Eisenberg 1988), the investigation of therapy effects on language processing in aphasia (e.g. Pulvermüller, Hauk, Zohsel, Neininger & Mohr 2005) and the possibility of using ERPs in clinical medicine (e.g. Connolly, D'Arcy, Lynn & Kemps 2000; Marchand, D'Arcy & Connolly 2002). Such clinical application of event-related potentials has been advocated both for the N1 (Hyde 1997), the MMN (Csepe & Molnar 1997; Näätänen 2003), and the P3 component (Polich 2004). In rehabilitation medicine, several potential areas of use exist: ERPs as tools for prognostic assumptions, for the assessment of functioning on the different linguistic levels, for longitudinal monitoring or even as therapeutic tools for cortical remodeling (Giaquinto 2004). ERPs can furthermore be useful in the assessment of cognitive functions as a supplement to neuropsychological methods (Mazzini 2004). A special advantage of this method is that it allows the investigation of cognitive processes even in patients who can not respond behaviorally (Näätänen 2003).

Auditory and speech sound processing in the human brain

Since the beginning of modern neuroscience in the 19th century, language processing in the brain has been proposed – based on lesion studies – to be localized mainly in the perisylvian areas of the left hemisphere (Broca 1861; Wernicke 1874). From these days

derives also the notion that anterior language areas mainly contribute to speech production and posterior areas mainly to comprehension (Wernicke 1874). In the majority of cases, patients with impairments predominantly in speech production (eg. Broca's aphasia, transcortical motor aphasia) have lesions in left inferior frontal cortex, while lesions in patients with severe comprehension difficulties (e.g. Wernicke's aphasia, transcortical sensory aphasia) are located in posterior regions of temporoparietal cortex (Goodglass & Kaplan 1983). Global aphasia with severe impairments of both speech production and comprehension usually is a result of a lesion of the entire perisylvian region, often due to infarction of the medial cerebral artery (Damasio & Geschwind 1984; Goodglass & Kaplan 1983). Lesions to areas connecting posterior with anterior language areas, i.e. lesions to cortical and subcortical structures in the medial temporal lobe, often cause problems with repetition despite fluent speech and mainly spared comprehension (conduction aphasia; Damasio & Geschwind 1984; Goodglass & Kaplan 1983).

Largely due to the emergence of modern neuroimaging techniques, research on auditory and speech sound processing has made large progress through the recent two decades. Some basic processing mechanisms have been clarified (for a review, see e.g. Cutler & Clifton Jr. 1999; Gazzaniga, Ivry, Mangun & Swaab 2002; Wise 2003), but still a number of open questions exist. One of the areas of dispute is whether the perception of speech sounds is immediately linked to their production as suggested by some researchers in the so-called motor theory of speech perception (see Liberman & Whalen (2000) for a revised version of the theory), or whether speech perception processes are independent of speech production, at least at the more basic processing levels.

Regardless of this question, there is agreement that cortical speech sound processing is initiated in the lateral superior temporal gyrus (STG). Essential contribution to the development of this understanding of basic auditory processing has come from monkey models (e.g. Kaas & Hackett 2000). In monkeys, primary auditory cortex consists of a core, a belt and a parabelt region which all are organized tonotopically. The core region gets its input from the medial geniculate complex and projects to the parabelt region where a second stage of primary auditory processing seems to take place. The parabelt receives input also from the thalamus and midbrain structures and is reciprocally connected to more remote areas of the STG.

Further processing from the auditory cortex seems to happen in two different streams which are reflecting different properties of the auditory input: a ventral ("what") and a dorsal ("where") stream (Kaas & Hackett 1999; Rauschecker & Tian 2000). There has been

some debate on the function of the latter stream which has been proposed to process 'where-in-frequency' rather than 'where-in-space' properties, i.e. aspects of spatial motion, also labeled 'how' processing (Belin & Zatorre 2000). Furthermore, the existence of more than one dorsal stream has been suggested (Wise, Scott, Blank, Mummery, Murphy & Warburton 2001). It seems however established that the ventral stream reflects more meaning-related properties, while the dorsal stream is more related to processing of phonetic and phonological features. In further elaborations of the dual route model, it has been suggested that only the dorsal stream has a close relation to speech production (Hickok & Poeppel 2004; Scott & Johnsrude 2003), thus adding a new aspect to the long-standing discussion about the motor theory of speech perception. It has furthermore been proposed that some degree of bi-directionality exists in both the ventral and the dorsal pathways (Hickok & Poeppel 2004; Hickok & Poeppel 2007).

Eventually, the streams are claimed to project to inferior prefrontal cortex, approaching Broca's area from a more ventral and a more rostral domain respectively. Broca's area can be subdivided into three regions where anterior parts of the inferior frontal gyrus (IFG) are suggested to mainly process semantic aspects of language while posterior superior parts of the IFG are more engaged in phonological processing (Bookheimer 2002), thus reflecting the two streams also at this processing level.

Regarding hemispherical specialization of speech sound processing, the traditional view is that the left hemisphere is specialized in language processing. This notion is mainly based on lesion studies (e.g. Broca 1861; Wernicke 1874), investigations of brain anatomy (e.g. Geschwind & Levitsky 1968) and results from neuroimaging research (e.g. Demonet et al. 2005; Wise 2003). The processing of rapid changing acoustic features is important in speech sound processing, and it has been suggested that the left STG is specialized for the processing and integration of rapid spectro-temporal changes (Efron 1963; Nicholls 1996; Zatorre 2001). These rapid changes are especially prominent in consonants, and it has been proposed that both hemispheres may contribute to the processing of vowels (e.g. Shankweiler & Studdert-Kennedy 1966). In another hypothesis, it has been claimed that a predisposition of the left hemisphere with regard to categorical processing and / or representation of acoustic information might make the left hemisphere better suited for the processing of phonemes (Liebenthal, Binder, Spitzer, Possing & Medler 2005).

Some researchers emphasize a bilateral representation of mechanisms of early speech sound processing claiming that two ventral streams exist in the abovementioned dual stream model and that both hemispheres are able to map meaning on sound (Hickok & Poeppel

2000; Hickok & Poeppel 2007). Arguments for this view are that almost all neurophysiological studies find bilateral temporal activation during passive perception of speech stimuli, and that the clinical presentation of severely impaired speech perception – pure word deafness – in the vast majority of cases is caused by bilateral damage to STG (see Hickok & Poeppel 2004 for a detailed discussion). The ventral streams are in this model claimed to be functionally different between the two hemispheres, and in opposition to the abovementioned temporal vs. spectral feature processing discrimination (Zatorre 2001), it is proposed in a so-called asymmetric sampling in time theory (Poeppel 2003) that neural mechanisms for integrating information over longer timescales are predominantly located in the right hemisphere, whereas mechanisms for integrating over shorter timescales might be represented more bilaterally (see also Abrams, Nicol, Zecker & Kraus 2008).

Auditory and speech sound processing in aphasia

In aphasia, deficits of input analysis have been suggested to occur at several linguistic levels, i.e. both in phonemic and in lexical-semantic processing (e.g. Cappa, Cavallotti & Vignolo 1981). Also impaired auditory non-speech processing has been demonstrated in aphasia which is not a surprising result as lesions often encompass primary auditory cortex (e.g. Robin, Tranel & Damasio 1990; Stefanatos, Braitman & Madigan 2007; Tallal & Newcombe 1978; Van Lancker D. & Sidtis 1992; von Steinbuchel, Wittmann, Strasburger & Szelag 1999). A large number of studies have investigated speech sound processing in aphasia and its relation to language comprehension problems (Baker, Blumstein & Goodglass 1981; Basso, Casati & Vignolo 1977; Baum 2002; Blumstein, Baker & Goodglass 1977a; Blumstein, Cooper, Zurif & Caramazza 1977b; Caplan, Gow & Makris 1995; Gandour & Dardarananda 1982; Jauhiainen & Nuutila 1977; Miceli, Caltagirone, Gainotti & Payer-Rigo 1978; Miceli et al. 1980; Milberg, Blumstein & Dworetzky 1988; Square-Storer, Darley & Sommers 1988; Tallal & Newcombe 1978; Varney 1984; Yeni-Komshian & Lafontaine 1983). Although aphasic groups generally show speech perception impairments when compared to healthy controls (Baker et al. 1981; Baum 2002; Blumstein et al. 1977a; Jauhiainen & Nuutila 1977; Miceli et al. 1980), the majority of the studies have not been able to show clear correlations between the severity of perceptual impairments and the severity of language comprehension problems (Basso et al. 1977; Blumstein et al. 1977a; Gandour & Dardarananda 1982; Milberg et al. 1988). In fact, such a correlation was shown in an aphasic group for the processing of non-verbal stimuli, but not for speech sound processing (Tallal & Newcombe 1978).

On the basis of these results, one can question the traditionally held opinion that language comprehension requires a sequence of processing steps starting with the processing of purely auditory parameters of the incoming signal, continuing with the analysis of speech sound specific parameters and eventually leading to the comprehension of clusters of speech sounds, i.e. words and sentences. On the other hand, one could argue that the abovementioned studies did not investigate online speech sound processing, but rather "meta-processing-skills" with regard to the subject's knowledge of speech sounds, and that the results thus do not contradict a sequential processing model. Furthermore, the traditional view of left-hemispherical specialization for speech sound processing has found support through the fact that the aphasic subjects mainly are impaired in the processing of consonants, but to a much lesser degree in vowel processing (Baker et al. 1981; Basso et al. 1977; Blumstein et al. 1977a; Blumstein et al. 1977b).

ERP studies of aphasia have revealed disturbed processing at several stages and in response both to speech and non-speech stimuli. N1 amplitude has been found reduced in aphasia in response to pure tones (Pool et al. 1989; Woods, Knight & Scabini 1993) and words (Rothenberger, Szirtes & Jürgens 1982). Investigating groups of patients with unilateral brain lesions where each group contained both left and right hemisphere damaged patients, Knight and coworkers found reduced N1 amplitudes in patients with lesions in STG, but not in patients with frontal or inferior parietal lobe lesions (Knight et al. 1980; Knight, Scabini, Woods & Clayworth 1988). The magnetic N1 response was found reduced or even absent in patients with large temporoparietal lesions, but not when the brain damage was located in the frontal lobe (Makela, Hari, Valanne & Ahonen 1991). In a recent study, bilateral N1 amplitude reduction in response to rich tones which were delivered monaurally to the right ear was observed over both hemispheres in a group of eight aphasic patients, seven of them having Wernicke's aphasia (Ilvonen, Kujala, Tervaniemi, Salonen, Näätänen & Pekkonen 2001). On the contrary, N1 amplitude in response to monaural left ear stimulation was not significantly reduced in these subjects (Ilvonen et al. 2001). In another study also with eight aphasic subjects using both speech and non-speech sounds as stimuli, no significantly reduced N1 amplitudes were observed (Ilvonen et al. 2004). When comparing left hemisphere damaged patients with aphasia with right hemisphere damaged patients and with healthy subjects, word-elicited N1 was reduced only in the aphasia group (Rothenberger et al. 1982). N1 amplitude was lateralized to the contralesional hemisphere in both patient groups (Rothenberger et al. 1982). A possible correlation between N1 latency,

amplitude or distribution and comprehension deficits in aphasia has not been investigated so far.

Unattended discrimination of auditory stimuli has been studied by a number of studies investigating the MMN component. Its amplitude has been found reduced in response to harmonically rich tones (Ilvonen et al. 2004; Ilvonen et al. 2001; Pettigrew et al. 2005), synthetic vowels (Aaltonen et al. 1993) and consonant-vowel (CV) syllables (Auther, Wertz, Miller & Kirshner 2000; Ilvonen et al. 2004; Pettigrew et al. 2005; Wertz, Auther, Burch-Sims, Abou-Khalil, Kirshner & Duncan 1998), at least in some aphasic subjects and for some of the stimulus contrasts investigated. In a first study, two aphasic patients with frontal brain lesions showed MMN to both pure tone pitch difference and to synthetic vowel contrast, while two patients with posterior lesions had an identifiable MMN only in response to the non-speech, but not to the speech stimuli (Aaltonen et al. 1993). Similar results were found by a study investigating 17 aphasic subjects with CV stimuli (Auther et al. 2000). In all three subjects with purely anterior lesions, an MMN response was observed, while the medial temporal lobe was the overlapping brain-damaged region for the seven subjects that did not show an MMN response (Auther et al. 2000). Ilvonen et al studied MMN responses elicited by harmonically rich tones of 25 ms and 50 ms duration compared to a standard 75 ms tone (Ilvonen et al. 2001). Differences between the aphasia group and healthy controls were found only for the 25 ms deviant: MMN amplitude was attenuated in the aphasia group over both hemispheres when the stimuli were presented to the right ear, but over the left hemisphere only when presented to the left ear (Ilvonen et al. 2001). The authors suggest that a lesion to the left STG affects MMN generators in both hemispheres (Ilvonen et al. 2001).

In a study that sought to investigate differences between non-speech and speech sound processing, significantly attenuated MMN amplitudes in an aphasia group compared to healthy controls were observed for vowel change and vowel length difference, while the change of harmonic tones that matched the speech standard and deviant stimuli with regard to acoustic properties did not lead to significant amplitude reductions, although a clear trend was observed (Ilvonen et al. 2004). The authors propose that the different response patterns are caused by separate neural substrates for speech vs. non-speech processing (Ilvonen et al. 2004).

The so far largest study of MMN in aphasia (n = 24) used pure tones differing in pitch and synthetic CVs and reported shortened MMN duration to both non-speech and speech stimuli while MMN amplitude was attenuated in response to the speech stimuli only (Wertz

et al. 1998). Furthermore, the duration of CV-elicited MMN correlated moderately with all clinical measures of aphasia that were used, leading the authors to the suggestion that duration of speech sound elicited MMN predicts aphasia severity (Wertz et al. 1998). In another study, MMN amplitudes in response to tonal stimuli differing in either frequency or duration and in response to real word deviant stimuli correlated strongly with results on the auditory comprehension section of the Western Aphasia Battery (Pettigrew et al. 2005). Also Auther et al (2000) observed differences with regard to auditory comprehension function: while eight of nine subjects with good auditory comprehension showed an MMN response, it was lacking in six out of eight patients with poor auditory comprehension. Other authors did however not observe a significant relationship between MMN disturbances and auditory comprehension (Aaltonen et al. 1993; Csepe et al. 2001).

Longitudinal ERP studies of aphasia are sparse, although already in 1972 the case of a global aphasic was reported who had no discernible N1 or P2 four days after stroke while both his language skills and his ERPs recovered over a seven months period (Kolman & Shimizu 1972). Cobianchi & Giaquinto (2000) investigated electrophysiological changes during rehabilitation in two cases of predominantly expressive aphasia and found that P300 improved during the observation period. Connolly et al. report a case of aphasia due to traumatic brain injury in which ERP assessment had a serious impact on the patient's rehabilitation program because preserved language comprehension could only be detected by ERPs, but not by standard clinical assessment (Connolly, Mate-Kole & Joyce 1999).

With regard to group studies with a longitudinal design, Ilvonen et al. investigated eight aphasic subjects four times during six months with tone-elicited mismatch negativity (Ilvonen et al. 2003). Initially, at four days after stroke onset, MMN amplitudes were reduced, but they improved during follow-up. Amplitude increase was correlated with improvement in clinical aphasia assessment. Interestingly, the largest MMN was found at three, but not six months post injury. In a recent study with 17 subjects, the development of passively evoked pure tone-P3 was investigated monthly during the first half year of aphasia rehabilitation (Nolfe, Cobianchi, Mossuto-Agatiello & Giaquinto 2006). Patients who showed the passive P3 component about two weeks after stroke improved significantly with regard to language comprehension – as opposed to patients without P3. Neither significant increase of passive P3 amplitude nor any coherent pattern of P3 restitution during the rehabilitation process was observed. Neurophysiological changes during a short-term intensive therapeutic intervention in nine patients with chronic aphasia have been studied by Pulvermüller and colleagues: The clinical improvement was reflected in an increase of an

early negativity (250 – 300 ms) elicited by words, but not pseudo-words, caused by bi-hemispherical activation changes (Pulvermüller et al. 2005).

Brain plasticity

Plasticity is an integral property of the brain in which its structure and function changes due to sensory input, motor act, association, reward signal, action plan, or awareness (Pascual-Leone, Amedi, Fregni & Merabet 2005). After brain damage, plasticity is of special importance as these structural and functional changes are the basis of recovery. Facilitated by the development and increased availability of functional neuroimaging during the past decades, the study of structural and functional changes in response to brain damage has been in focus, and an increasing amount of knowledge about post-damage plasticity has been gained. Besides scientific interest, a main clinical rationale behind this line of research is the hypothesis that some plastic changes after brain damage are correlated with successful recovery – or rather might be its precondition. Identifying this "successful plasticity" and possible therapeutic methods facilitating it, potentially opens a new and promising approach in neurorehabilitation (Cramer 2008a; Duffau 2006).

Several mechanisms of plasticity have been proposed, but the contribution of these mechanisms to neural reorganization after brain damage remains unclear for the time being (for an overview, see e.g. Duffau 2006 or Cramer 2008b). At a microscopic level, one mechanism is the functional modulation of synaptical strength through processes such as long term potentiation (LTP, Bliss & Lømo 1973). Structural changes at the microscopic level such as axonal sprouting are also involved in neuronal remodeling (Lamprecht & LeDoux 2004). Another proposed mechanism is the activation of so-called silent synapses which can become functional if their inhibition is suppressed (Malenka & Nicoll 1997). This mechanism is claimed to be especially important for short-term plasticity (Blitz, Foster & Regehr 2004). Only in recent years has it become evident that neuroglia not only provides neurons with 'resources' as energy and oxygen, but also directly modulates signal processing (Fields & Stevens-Graham 2002). Also very recently – contradicting the traditional view that new neurons do not occur in the adult human brain – neurogenesis has been demonstrated in humans (Steindler & Pincus 2002).

At the macroscopic level, functional changes can occur in areas remote to the focal brain lesion (so-called diaschisis; von Monakov 1914). Although diaschisis originally was thought to worsen the effects of a brain lesion, the contribution of diaschisis to the restoration of function after brain damage has also been claimed (Seitz, Azari, Knorr, Binkofski, Herzog

& Freund 1999). Another mechanism is the reorganization within functional networks: assuming that a certain brain function is spread over several brain areas, those areas of the network that are not affected by the lesion are reorganized improving function. Such reorganization might involve perilesional areas or remote areas in the ipsi- or even the contralesional hemisphere. Based especially on results from investigations of blind and deaf subjects, another mechanism has been suggested: cross-modal plasticity, i.e. the transfer of a brain function from one functional network to another (Kujala, Alho & Näätänen 2000).

A number of studies have investigated brain activity in relation to language processing in aphasia. Their results illustrate that reorganization of structure and function through the expression of neural plasticity plays a crucial role in recovery of language (for a review, see Marsh & Hillis 2006). Language related plasticity can be influenced by a number of parameters such as lesion localization (e.g. Breier et al. 2004; Heiss, Kessler, Thiel, Ghaemi & Karbe 1999), time after brain injury (e.g. Cardebat et al. 2003; Ilvonen et al. 2003; Saur et al. 2006), prognosis / outcome (e.g. Heiss & Thiel 2006), etiology (e.g. Breier, Billingsley-Marshall, Pataraia, Castillo & Papanicolaou 2006), age (cf. Breier et al. 2006), or treatment (e.g. Leger et al. 2002; Meinzer, Elbert, Wienbruch, Djundja, Barthel & Rockstroh 2004; Musso, Weiller, Kiebel, Muller, Bulau & Rijntjes 1999; Pulvermüller et al. 2005; Small, Flores & Noll 1998). Not only topographic distribution of brain activity related to language processing, but also its timing can undergo plastic reorganization in aphasia (Angrilli, Elbert, Cusumano, Stegagno & Rockstroh 2003). Even different brain activity patterns with regard to whether correct answers or paraphasias are produced in a naming task in a single aphasic patient, have recently been demonstrated (Meinzer et al. 2006). Furthermore, in patients with reduced syntactic processing, increased semantic processing activity has been shown in a syntactic task, possibly reflecting a compensational mechanism and suggesting plasticity between linguistic levels (Hagoort et al. 2003).

A central question in neuroimaging research of plasticity in aphasia has been the role of the non-language dominant hemisphere for recovery from aphasia (for reviews, see Herholz & Heiss 2000; Rijntjes & Weiller 2002). While some investigators have stressed the importance of the contralesional hemisphere (Blasi, Young, Tansy, Petersen, Snyder & Corbetta 2002; Cappa et al. 1997; Crinion & Price 2005; Leff, Crinion, Scott, Turkheimer, Howard & Wise 2002; Musso et al. 1999; Thomas, Altenmuller, Marckmann, Kahrs & Dichgans 1997; Thulborn, Carpenter & Just 1999; Voets et al. 2006), others underline the importance of ipsilesional structures for successful outcome (Breier et al. 2004; Heiss et al. 1997; Heiss et al. 1999; Karbe, Kessler, Herholz, Fink & Heiss 1995; Rosen et al. 2000;

Warburton, Price, Swinburn & Wise 1999; Winhuisen et al. 2005). Probably, a major reason for the diverging results is the circumstance that aphasia of course is not the result of the impairment of just one cerebral process. A variety of basic cognitive processes is involved in language production and comprehension and can potentially be dysfunctional in aphasia. Although refined study designs allow the assignment of small brain areas and networks to defined basic processing steps involved in language, large parts of the brain are usually activated when speaking or listening to speech (cf. Demonet et al. 2005).

Changes of brain activity over time are another correlate of plasticity. Such changes in patients recovering from aphasia have recently been demonstrated using ERPs (Ilvonen et al. 2003; Nolfe et al. 2006), EEG (Hensel, Rockstroh, Berg, Elbert & Schönle 2004), positron emission tomography (PET; Cardebat et al. 2003; de Boissezon et al. 2005) and functional magnetic resonance imaging (fMRI; Crosson et al. 2005; Saur et al. 2006). These investigations indicate that there is not just a slow increase of activation in line with the recovery of language function, but that complex patterns exist including sophisticated hemispherical changes (Saur et al. 2006) and transient hyperactivation (Ilvonen et al. 2003; Saur et al. 2006). Transient hyperactivation has also been reported in patients with successful motor recovery (Tombari et al. 2004).

Aims of the study

General aims and research questions

On the background of possible clinical use of event-related potentials in aphasia rehabilitation, the present study pursues the following two principal aims:

- To investigate acoustic and speech sound processing in aphasia in order to shed more light on the nature of auditory comprehension deficits in aphasia.
- To investigate plasticity after brain injury and mechanisms of aphasia recovery.

Based on these aims and the unclear contribution of sound processing deficits to language comprehension impairments in aphasia (cf. page 17), a number of research questions are investigated in the papers of this present study:

(1) Which processing steps are disturbed? (papers I – IV)
(2) Are there differences with regard to non-speech vs. speech sound processing? (papers I and IV)
(3) Are there differences with regard to unattended vs. attended speech sound discrimination? (Comparative analysis of passive vs. active processing)
(4) Are observed changes due to aphasia or due to a more general effect of brain damage? (paper IV)
(5) Does changed auditory and speech sound processing relate to the function of language comprehension as assessed by clinical aphasia tests? (papers I – IV)
(6) Is the topographical distribution of activity altered in aphasia? (papers I – IV)
(7) Do patterns of activity and / or its topographical distribution change during recovery from aphasia? (paper III)
(8) Which ERP components are (most) applicable regarding potential clinical use? (papers I – IV)

General research strategy

The principal approach of this study is to neurophysiologically investigate auditory processing in patients with impaired language comprehension as measured by clinical aphasia assessment. To enlighten the relevance of changes in acoustic processing for language comprehension, the following main research strategies are pursued:

- We study both speech and non-speech sound processing.
- We look for differences in ERP parameters between brain injured subjects and healthy controls.
- We look for differences in ERP parameters between brain injured subjects with and without aphasia, respectively with left- and right-hemisphere lesions.
- We search for interactions between changed tonal vs. speech sound processing and brain injured subjects with or without aphasia (i.e. with left- or right-hemisphere lesions).
- We search – in aphasic subjects – for correlations between ERP parameters and language comprehension as measured by clinical aphasia assessments.
- We group aphasic subjects regarding language comprehension impairment and look for differences in ERP parameters between these groups.
- We study aphasic subjects during recovery and search for correlations between improvement in language comprehension and changes in ERP parameters.

Methods, materials and subjects

Study designs

Pursuing the abovementioned aims, studies I, II, and III were designed in a more explorative fashion investigating a group of patients and exploring electrophysiological parameters and their relation to personal and clinical data. Study IV was designed to test hypotheses that were established on the background of results from study II.

Papers I, II, and IV are cross-sectional studies comparing a group of aphasic patients with a group of healthy controls, in study IV additionally with a group of non-aphasic, right-hemisphere damaged patients. Paper III is based on a longitudinal design by investigating a group of aphasic subjects at two time points during their rehabilitation process.

The selection process used in the studies is not designed to study a representative selection of the general aphasia *population*. However, an attempt is made to cover a wide range of *aphasic disorders* in order to investigate its different facets. This is probably achieved to a larger degree in studies I and II than in papers III and IV, due to the smaller sample size in the latter studies.

Subjects

The main inclusion criterion for the primary study subjects was the presence of impaired language comprehension due to brain damage acquired at an age when normal language development was completed. Inclusion criteria relevant for all participating subjects were: native speaker of Norwegian and age over 16 years. All control subjects were right-handed. Exclusion criteria were: hearing problems, craniectomy, history of psychological or psychiatric consultation of more than six months duration or inward psychiatric treatment, history of language problems (e.g. stuttering, dyslexia), and history of supraspinal neurological disorders.

Aphasic subjects and brain-damaged controls (paper IV) were consecutively recruited from patients admitted to our hospital for rehabilitation. After admission, the patient's charts were checked with regard to in- and exclusion criteria. When the patients were found to fill the criteria, they were asked to participate. In addition to the chart-check, subjects or their relatives were asked to complete a form with regard to in- and exclusion criteria. A second chart-check was performed after discharge to check for exclusion criteria possibly detected first during the rehabilitation stay (e.g. hearing problems).

The healthy controls were recruited from hospital staff, from inward patients admitted to the hospital for other reasons than brain damage, and from relatives of the aphasic patients. Written informed consent was obtained from all participating subjects. The study was approved by the Regional Ethics Committee of Eastern Norway; approval with regard to statutory data privacy requirements was given by the Norwegian Social Science Data Services.

Many of the participating aphasic subjects were quite severely impaired; the mean age of the present sample is lower than in an unselected sample of aphasic patients. This is due to the fact that Sunnaas Rehabilitation Hospital is specialized in rehabilitation of more complex and severe cases of brain injury and rather young adults. However, a rather large range of auditory comprehension impairments was covered in papers I to III, but to a lesser degree in paper IV.

Assessment of aphasia and of auditory comprehension function

The aphasic participants were examined with the Norwegian Basic Aphasia Assessment (Norsk grunntest for afasi, NGA; Reinvang 1985b). The NGA is the only general aphasia assessment validated for Norwegian and is widely used all over Norway. It contains subtests for auditory comprehension, repetition, naming, reading comprehension, reading, syntax, and writing skills. Both the total NGA score and the subscore for auditory comprehension were used as measures of aphasia severity. As a second clinical aphasia measure, the Token test was used (De Renzi & Faglioni 1978; De Renzi & Vignolo 1962). The participants of study IV were in addition examined with the Boston Naming Test (Goodglass, Kaplan, Weintraub & Segal 2001).

To assure that the control subjects had no sub-clinical language impairments, they were investigated using the auditory comprehension part of the NGA and the Token test (and the Boston Naming test in paper IV).

Clinical and lesion data

Clinical data regarding date, etiology, and localization of the lesion as well as neuropsychological findings were extracted from the patient's medical charts. Details are described in each paper, but in general, the majority of the patients were investigated within the first year post injury (although rather large variation was present) and cerebrovascular accidents were the reason for their lesions. All patients showed other neuropsychological impairments in addition to aphasia, most commonly apraxia, memory, or attention disorders.

CT and MR scans were performed as part of the clinical routine; their results were evaluated in order to determine which lobes were affected by the individual lesions. While some few patients also had occipital lesions, the majority of the lesions affected the frontal, temporal and / or parietal lobes.

Stimuli

Non-speech and speech stimuli were used. The two stimulus types (speech vs. non-speech) did not differ only with regard to their 'speechness', but natural speech sounds were contrasted with tone stimuli where the deviants differed from the standard stimuli in one of the basic parameters duration or frequency. Thus, this study does not investigate differences around a precise border that discriminates whether a stimulus is perceived as purely acoustic or as speech stimulus, but looks into typical speech sound processing on the one hand and into the processing of basic acoustic features on the other.

As speech sound stimuli, natural syllables were chosen. The Norwegian syllables /ba:/ and /ta:/ were digitally recorded from a middle-aged female native speaker of the standard East-Norwegian dialect. In order to obtain the same stimulus length (245 ms), the recorded syllables were cut and re-spliced at zero-crossings of the steady-state vowel. An 8 kHz low-pass filter and Hanning windows with 20 ms fall / rise times were applied. Although the use of natural speech sounds allows less control over different stimulus parameters, they were considered to be more suitable for an investigation of the relevance of speech sound impairments for auditory comprehension function than synthesized stimuli.

The tone stimuli used in papers I and III were harmonically rich tones differing in duration (75 vs. 25 ms). They were chosen because the stability and the test–retest reliability of this paradigm have been demonstrated earlier (Joutsiniemi et al. 1998; Tervaniemi, Lehtokoski, Sinkkonen, Virtanen, Ilmoniemi & Näätänen 1999) and because they have been previously used in aphasia research (Ilvonen et al. 2003; Ilvonen et al. 2001; Pettigrew et al. 2005). The tones consisted of three frequency components (0.5, 1, and 1.5 kHz); the second and third components were respectively 3 and 6 dB lower in intensity than the first one. In paper IV, the tone stimuli were pure tones of 50 ms duration differing in pitch (1 vs. 2 kHz). For details of stimuli and paradigms used in the four papers, see tables 2a and 2b.

Table 2a: Stimulus paradigms

Paradigm	Tones passive	Syllables passive	Syllables active	Tones active
Stimulus type	harmonically rich tones	natural speech sounds	natural speech sounds	pure tones
Standard stimulus	0.5, 1, and 1.5 kHz 75 ms	/ba:/ 245.9 ms	/ba:/ 245.9 ms	1 kHz 50 ms
Deviant / target stimulus	0.5, 1, and 1.5 kHz 25 ms	/ta:/ 245.2 ms	/ta:/ 245.2 ms	2 kHz 50 ms
p deviant / target	10 %	15 %	15 %	15 %
SOA[a]	350 ms	600 ms	1.5 s	1.5 s
Total stimulus number	2000	1042	205	200

[a] Stimulus onset asynchrony: time from onset of a stimulus to onset of the next stimulus.

Table 2b: Paradigms used in the different papers

	Paper I	Paper II	Paper III	Paper IV
Paradigms	passive tones and syllables	active syllables	passive tones and syllables active syllables	active tones and syllables
ERP components investigated	MMN	N1, P3, N2	MMN, N1, P3, N2	N1, P3, N2

ERP recording

The neurophysiological investigations were performed at the ERP lab at Sunnaas Rehabilitation Hospital. EEG was recorded using a Synamps II amplifier and Scan 4.3 software (Neuroscan). In studies I – III, a free electrode montage was used; in study IV, electrodes were mounted with a cap (EasyCap). Electrode impedances were controlled before recording and held below 5 kΩ. A nose-reference was used. EEG was recorded at the following electrode sites, according to the 10-20-system (Jasper 1958): Fp1/2, F7/8, F3/4,

T3/4, C3/4, T5/6, P3/4, O 1/2, M1/2. In addition, vertical and horizontal electrooculograms were recorded to allow removal of ocular artifacts.

Stimuli were presented binaurally via headphones at approximately 80 dB SPL using the STIM audio system (Neuroscan). Subjects were seated in a rest chair or their wheel chair in a silent environment and were requested to avoid unnecessary movement. In the passive, unattended paradigms, subjects were instructed to leaf through richly illustrated magazines, while they had to push a button (STIM Response Pad) in response to target stimuli in the active, attended paradigms. Before recording during the active discrimination tasks, the stimuli were presented to the subjects for a short rehearsal period.

Statistical analysis

Common methods of ERP quantification and statistical analysis were applied (cf. Handy 2005; Picton et al. 2000); details are described in each paper. In general, for each subject, average files were calculated for each paradigm and stimulus separately. During this process, a band-pass filter was applied and the EEG-recordings were visually evaluated with regard to their general quality; they were furthermore corrected for ocular artifacts (according to Semlitsch, Anderer, Schuster & Presslich 1986) and parts containing especially low or high amplitudes were excluded from further analysis. The averaged files were corrected for pre-stimulus baselines. For each paradigm, it was assured that a sufficient number of sweeps was acquired from each individual subject in order to obtain a satisfactory signal-to-noise ratio: in the active paradigms, a minimum of 75 % of the stimuli had to be available for analysis; in the passive paradigms, a limit of 60 % was set (cf. table 3). Some subjects were excluded in whom only an insufficient number of sweeps could be obtained.

Table 3: Numbers of sweeps for deviant / target stimuli
Groupwise mean numbers of sweeps (for deviant / target stimuli) used for statistical analysis. Lowest individual sweep numbers in parentheses. Total number of deviant / target stimuli presented in each paradigm, is given in parentheses in the header row.

Table 3a: Paper I

	Tones passive (total 200)	**Syllables passive (total 150)**
Aphasia	189 (156)	128 (101)
Control	188 (178)	119 (93)

Table 3b: Paper II

	Syllables active (total 30)
Severe aphasia	29 (26)
Moderate aphasia	28 (24)
Control	29 (27)

Table 3c: Paper III

	Tones passive (total 200)	Syllables passive (total 150)	Syllables active (total 30)
Session 1	186 (162)	128 (113)	29 (24)
Session 2	186 (174)	133 (113)	27 (25)

Table 3d: Paper IV

	Tones active (total 30)	Syllables active (total 30)
Aphasia (LHD)	28 (25)	28 (23)
Non-aphasia (RHD)	28 (24)	27 (23)
Healthy control	28 (24)	28 (24)

Main ERP parameters analyzed in this study were peak latencies and mean amplitudes. First, time windows were determined in which individual peak latencies were determined. These were then averaged to a group latency which served as the center of time windows to calculate individual mean amplitudes for a given ERP component. These individual mean amplitudes were then used for statistical analysis. The determination of individual latencies and the calculation of mean amplitudes were carried out using READPEAK.EXE 2.0 software. SPSS 11.0 software was used for statistical analysis. For the analysis of some waveforms, a time-window approach was used.

The main statistical method used was analysis of variance (ANOVA) which allows analyzing for differences in ERP parameters between groups and for differences in further factors within the groups. ANOVA-details are described in each paper. Correlations

between ERP parameters and clinical data (e.g. aphasia assessment scores, time post injury) were analyzed using the Spearman Rank test.

Summary of papers

Paper I

A group of aphasia subjects (n = 18), studied at on average three months after brain injury, showed subtle changes in topographic distribution of MMN to tonal and phonemic stimuli when compared to a healthy control group (n = 11). While tone-elicited MMN was right-lateralized and syllable-elicited MMN left-lateralized in the control group, the topographic pattern was more centralized in the aphasic group. In addition, MMN was more frontally located in the aphasia compared to the control group. The results regarding speech sounds are consistent with a reduced left temporal lobe processing contribution and increased right hemisphere activation. The participants represented a wide range of severity in auditory comprehension as assessed with a standardized aphasia test, but no significant amplitude reductions were observed and MMN parameters were not correlated with aphasia test results. Automatic phoneme discrimination as such may be critical for speech perception, but not sufficient for auditory language comprehension, and may play a limited role in aphasic comprehension deficits.

Paper II

Attended speech sound processing in aphasia was investigated with event-related potentials during a syllable detection task. As the healthy control group (n = 11), the aphasic subjects were able to perform the task almost without errors, but the latter group had slowed behavioral responses. Processes related to target identification (P3) were not significantly attenuated in the aphasia groups. However, electrophysiological components reflecting primary stimulus analysis (N1) and attended stimulus classification and discrimination (N2) had significantly reduced amplitudes indicating reduced processing, especially in the severe (n = 10) compared to the moderate (n = 10) aphasic subjects. Furthermore, N1 amplitude reduction correlated with lower scores in clinical aphasia assessment.

The ERP results reveal a reduction of language-related processing in the aphasic subjects which however did not prevent them from performing the task correctly. In the aphasic subjects, altered stimulus processing in early time windows (N1, N2) has adverse consequences for auditory comprehension of complex language material as assessed by clinical aphasia tests, while the simpler task of syllable detection was not impaired. The

aphasic subjects might have discriminated the stimuli by increased reliance on acoustic differences.

The degree to which compensational patterns of speech sound processing can be activated probably varies depending on lesion site, time after injury, and language task.

Paper III

In a longitudinal study, eight patients with aphasia reflecting a wide range of auditory comprehension impairment were investigated at about three and seven months post injury. Token test and Norwegian Basic Aphasia Assessment revealed a statistically significant, but clinically rather insignificant improvement in auditory comprehension function during the observation period. MMN, N1, N2, and P3 amplitudes and latencies did not change significantly between sessions, but a significant shift of topographical distribution from the contralesional to the ipsilesional hemisphere was observed for the N2 component. In addition, the study of individual waveforms indicated inter-individual differences in reorganization after brain injury.

Hemispherical distribution of brain activation in correlation to speech sound processing in aphasia can change during the first months after brain injury. ERPs are a potentially useful method in detecting individual activation patterns relevant for recovery in aphasia rehabilitation.

Paper IV

Comparing ten aphasic subjects with ten non-aphasic subjects with right hemisphere lesions and with 18 healthy controls, ERPs were measured during two oddball paradigms in which the participants had to discriminate (i) tones differing in pitch and (ii) syllables differing in the initial consonant. Despite of some more errors and prolonged response times, the aphasic subjects were able to perform the task successfully. N1 amplitude was reduced in both brain damaged groups when elicited by tones, but in response to speech sounds only in the aphasia group. N1 right hemisphere lateralization was larger for syllables compared to tones in the aphasia group. Also delayed N2 and P300 latencies and reduced P300 amplitudes in response to syllables were observed in the aphasic subjects.

In addition to disturbances of non-linguistic auditory processing, specific impairments in speech sound processing seem to occur already at 100 ms post stimulus in aphasia. The observed topographical distribution indicates right hemisphere involvement specific to speech sounds.

Both in paper II and in paper IV, successful syllable discrimination was observed despite of reduced feature analysis activity (N1 amplitude reduction). While this came along with reduced stimulus discrimination activity (N2 amplitude reduction) in the aphasic groups in paper II, it occurred together with delayed stimulus discrimination (prolonged N2 latency) and delayed target identification activity (prolonged P300 latency) in the aphasia group in paper IV. Thus, it is suggested that reduced early feature analysis can be compensated for by different patterns of cognitive processing: reduced processing activity or delayed processing, both mechanisms leading to successful stimulus discrimination.

Comparative analysis of passive vs. active processing

Paper I investigated passive speech sound discrimination, and paper II active discrimination of the same syllables. Since a number of subjects (several patients and all controls) participated in both studies, a comparative analysis could be performed.

Table 4 gives an overview of the two groups which were not significantly different with regard to sex distribution, age or education. The aphasia group represents a wide range of disturbed auditory comprehension.

Table 4: Comparative analysis of active vs. passive syllable processing – subject and clinical data

	Aphasia	**Control**
n	9 female, 9 male	6 female, 5 male
Age	53.2 (18.0 – 66.9)	58.2 (33.0 – 74.1)
Years of education	12.9 (9 – 20)	13.8 (10 – 18)
Token test *	16 (1 – 32)	34 (31 – 35)
NGA auditory comprehension **	53 (13 – 70)	71 (71)
NGA total score ***	145 (35 – 209)	-
Months after brain injury	9.6 (0.8 – 97.7) median: 3.6	-

Mean values are shown, observed min. and max. values in parentheses.

* max. possible score ca. 36 (depending on years of education)

** max. possible score 71

*** max. possible score 217

Figure 1 and table 5 show that similar behavioral results were found for this sample as for the one from paper II: The aphasic subjects were able to detect the target syllables, but showed significantly prolonged reaction time (RT).

Figure 1

Target syllable detection in active discrimination paradigm. Mean reaction time (box) and SD (bar) for the aphasia (black) and the control group (grey) illustrating the significant RT increase in the aphasia group.

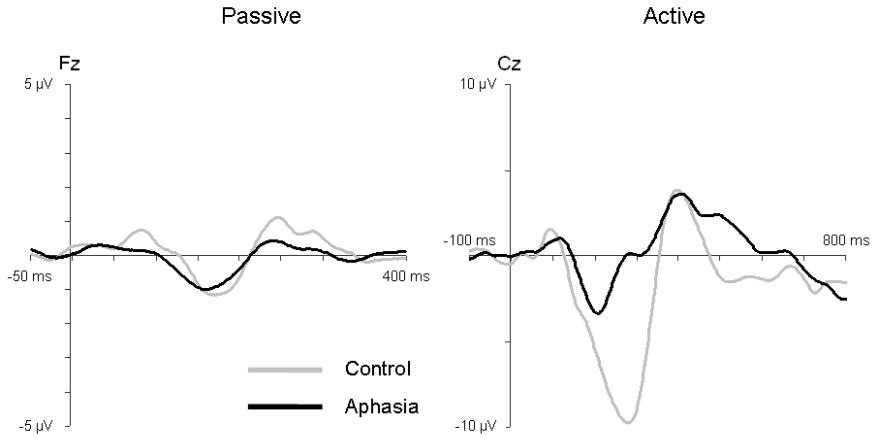
Table 5: Comparative analysis of active vs. passive syllable processing – behavioral results for target syllable detection

	Aphasia	**Control**	
Reaction time (ms)	531 (SD: 219)	383 (SD: 73)	p = 0.02
Hits	29.8 (29 – 30)	30 (-)	p = 0.08
False alarms	1.3 (0 – 4)	0.7 (0 – 2)	p = 0.23

Mean values are shown, observed min. and max. values in parentheses (for reaction time: standard deviation (SD)).

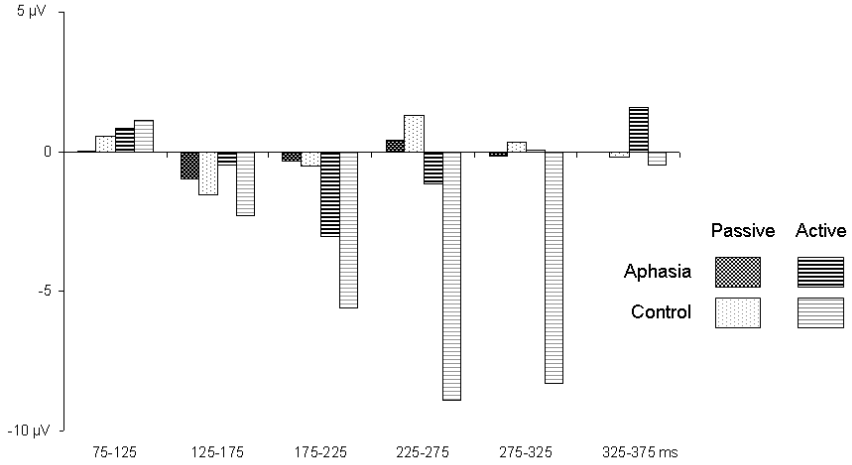
Figures 2 and 3 contrast the ERP results from the passive and the active syllable discrimination paradigms (/ba/ vs. /ta/). An ANOVA of ERP mean amplitudes in 50 ms time windows with the between factor *group* and the within factor *task* (passive vs. active) results in between effects for the three time windows between 175 and 325 ms (table 6). Task * group interactions are found in the same timeframe (table 6). When analyzing each paradigm separately, only in the active paradigm between group effects are observed.

Figure 2



Grand average waveforms for the aphasia (black) and the control group (grey) show minor differences for passive (left), but substantial changes in the aphasia group for active (right) syllable discrimination.

Figure 3



Bars representing mean ERP amplitudes in 50 ms time windows for passive (dots) and active (stripes) syllable discrimination (aphasia group: black; control group: grey). While there are no larger differences neither between groups nor tasks in the first intervals, from 175 ms on, active discrimination amplitudes increase in the control, but not in the same manner in the aphasia group.

Table 6: Comparative analysis of active vs. passive syllable processing – significant ANOVA effects

	Between group effect Overall	Task * group interaction	Between group effect Passive	Between group effect Active
175 – 225ms	F=4.74, p<0.05	F=4.35, p<0.05	F=0.24, p=0.63	F=4.99, p<0.05
225 – 275ms	F=10.94, p<0.01	F=23.19, p<0.001	F=1.83, p=0.19	F=17.33, p<0.001
275 – 325ms	F=11.87, p<0.01	F=16.00, p<0.001	F=4.30, p<0.05	F=14.00, p<0.001

ANOVA results from the comparative analysis of active vs. passive syllable processing using the between factor group (aphasia vs. control) and the within factor task (active vs. passive). Mean amplitudes from 50 ms time windows were analyzed. Only time windows where significant ANOVA effects were observed are shown.

General discussion

In the following, the main findings are discussed with emphasis on summarizing and comparing the individual papers on the background of the abovementioned research questions (page 25). First, those processing steps which were found disturbed in aphasia are shortly summarized before different aspects of the processing of speech sounds are discussed (tonal vs. phonetic, unattended vs. attended processing, relation to overall language function, specificity for aphasia). Subsequently, other subjects are focused upon: plasticity, processing changes over time, components of special interest with regard to clinical use, and methodological issues.

Disturbed processing steps

A number of cognitive processes are involved in the processing of auditory stimuli when the brain is, for example, listening to speech or performing a syllable discrimination task. In this ERP study, we investigated – in chronological post-stimulus order – the following processing steps: early integration of stimulus features (as reflected by the N1 component), automatic detection of differences between stimuli (MMN or N2a), attended stimulus discrimination and classification (N2) and target stimulus recognition (P300).

In summary, we find significantly reduced activity related to early stimulus feature integration (N1, papers II and IV), to later active stimulus discrimination and classification (N2, paper II) and to target detection (P300, paper IV) in the aphasic groups investigated. On the other hand, passive stimulus discrimination activity (MMN, paper I) was not significantly reduced. However, non-significant MMN amplitude reductions in response to syllables were observed, especially at ipsilesional fronto-central sites. Although ERP components may be used to operationalize processing stages, they probably also reflect overlapping cognitive and linguistic processes.

The fact that there was no significant MMN amplitude reduction in response to CVs in our aphasia group is conflicting with results from other studies (Auther et al. 2000; Ilvonen et al. 2004; Ilvonen et al. 2001; Pettigrew et al. 2005; Wertz et al. 1998). Several factors might have contributed to the fact that no significant reduction was observed: group composition, properties of the stimuli used (natural speech sounds, rather large phonetic differences between standard and deviant), the fact that stimuli were delivered binaural, and the mean time between brain injury and ERP recording (see paper I, page 77, for a detailed discussion).

Disturbances in electrophysiological parameters were observed despite of successful performance of the behavioral task of syllable discrimination (papers II and IV). In the aphasic groups from both papers, activity related to primary stimulus analysis (N1) was reduced. Interestingly, different electrophysiological patterns regarding later processing stages were observed: while the moderate and the severe aphasia group of paper II showed reduced active discrimination and classification processing (reduced N2 amplitudes), this activity was not reduced, but delayed in the aphasia group of paper IV. These different patterns might be the expression of different mechanisms that lead to successful task performance compensating for early feature analysis disturbances.

When considering the results of group studies, one has to bear in mind that different dysfunctions of auditory processing can lead to impaired language comprehension. Furthermore, language impairment needs not be caused by just one deficient process in the individual subject. In fact, comprehensive case studies have illustrated that several processes can be disturbed in one patient (Kraus et al. 1993; Strauss Hough et al. 2003).

Tonal vs. phonetic processing

Tonal vs. speech sound processing was compared with regard to passive discrimination (paper I) and active discrimination (paper IV) of stimuli. While the speech sound stimuli were the same in these two studies, they were contrasted to harmonically rich tones differing in duration in paper I and to pure tones differing in pitch in paper IV.

This present study could not find differences in MMN amplitudes with regard to speech vs. non-speech processing, of course mainly due to the fact that there was no significant MMN attenuation at all. Regarding previous research, several studies have reported MMN amplitude reductions specific for speech sounds, but not in response to tones: Aaltonen and coworkers found MMN elicited by pure tones differing in frequency in two aphasic subjects with posterior lesions, while synthesized vowel change did not elicit an MMN in these patients (Aaltonen et al. 1993). Two patients with anterior lesions had MMN responses both to the pure tones and the vowel stimuli (Aaltonen et al. 1993). Csépe et al reported resembling results when they observed no differences between four aphasic subjects and four healthy controls for MMN in response to pure tones differing in pitch, but observed MMN abnormalities in the same aphasic subjects when the stimuli were natural vowels or CVs (Csepe et al. 2001).

In another study, speech stimuli were composed of a natural consonant and synthetic vowels, while non-speech sounds were harmonically rich tones that were synthesized in a

process that resulted in non-speech stimuli that were acoustically similar to the speech stimuli (Ilvonen et al. 2004). The eight aphasic subjects participating in this study showed significant MMN amplitude reductions for the speech stimulus MMN which was elicited by differences in vowel phoneme or vowel length (Ilvonen et al. 2004). Although no significant MMN amplitude reductions for frequency or duration differences of the non-speech stimuli were found, a clear trend was observed also for these stimuli (Ilvonen et al. 2004). Significant MMN amplitude reduction has been observed also for harmonically rich tone duration change in a study investigating six aphasic subjects (Pettigrew et al. 2005). As there are reports of MMN amplitude reductions even to purely sinusoidal sounds in aphasia (Wertz et al. 1998), no straightforward double dissociation between tonal and speech sound MMN on one side and aphasia vs. non-aphasia on the other side seems to exist. Taking into account the fact that it is difficult to establish the exact border between tonal and speech sound processing, this seems reasonable. This borderline – if it exists – is still to be exactly defined. A recent study suggests that whether sounds are processed as phonemic units is depending on the context they are presented in rather than purely on their physical or phonological properties (Shtyrov, Pihko & Pulvermüller 2005).

Another aspect is the circumstance that MMN in principle is a measure of auditory sensory memory elicited by speech as well as non-speech stimuli (Näätänen et al. 2005). Although MMN responses specific for phonetic processing can be demonstrated with appropriate paradigms and especially using the MEG method (e.g. Näätänen et al. 1997), the MMN mechanism itself (as the other processes investigated in this study) is not specific for language processing. This might make the differentiation of tonal vs. speech sound processing deficits in aphasia using the ERP method difficult. However, differences in topographical distribution between tonal vs. speech sound MMN as also observed in this present study (paper I) indicate that at least some of the brain processes that elicit MMN are specifically related to (or maybe rather: prototypical for) speech and non-speech processing respectively.

Concerning active processing (paper IV), there are no other studies to our knowledge that compare tonal vs. speech sound processing in aphasia. With regard to stimulus feature analysis (N1, paper IV), we observed the opposite result compared to the MMN findings, namely significant N1 amplitude reductions in the aphasia group in response to both tones and stimuli. No stimulus effect was found, but a difference between tonal and speech sound processing in the aphasia group came to its indirect expression through a significant N1

amplitude reduction in response to both stimulus types in the aphasia group, but only in response to tones in the non-aphasia group.

Results for active tonal vs. speech sound discrimination activity (N2, paper IV) resemble the MMN findings in that no significant amplitude reductions were observed in the aphasia group for neither of the stimulus types, but here peak latencies were prolonged for both tones and speech sounds. On the other hand showed the aphasia group significantly reduced target detection activity (P300, paper IV) in response to syllables only and an almost significant stimulus effect was observed in this group ($p = 0.065$). The aphasic group's amplitude reduction however occurred together with slowed processing (prolonged RT as well as N2 and P300 latency) to both stimulus types. It would be very interesting to know whether the observed N2 amplitude reduction in the aphasic groups of paper II was specific for speech sound processing, but this question remains unsolved.

With regard to topographical distribution, a number of differences between tonal vs. phonetic processing were observed. A more posterior peak of speech sound processing activity compared to tonal processing was observed for the MMN, the N1 and the N2 component both in the healthy control and the aphasia groups, although there were some differences between the groups in whether this effect was significant or not. This indicates that the gross processing structure is preserved in aphasic processing even when substantial activity reductions are observed.

Hemispherical processing differences are discussed in detail below (page 48), but with regard to the question of differences of tonal vs. speech sound processing, results for the aphasia groups regarding MMN and N1 indicate stimulus-specific topographical distribution with contralesional activation increase specific or larger for speech sounds.

In conclusion, this study suggests that differences between tonal and speech sound processing seem to exist in aphasia in early stimulus feature processing. At later processing stages, reduced target identification activity specific to speech stimuli was observed in an aphasic group (paper IV), but the same syllable stimuli did not lead to reduced target detection activity neither in the severe nor the moderate aphasia group of paper II.

The neural basis of passive vs. active stimulus discrimination

Attended processing of sublexical units has not been studied with ERPs in aphasia earlier. In studies using pure tone stimuli, reduced novel- and target-N2 was observed in brain injured patients with lateral and inferior parietal lesions, but was found unaffected by temporal lesions (Knight et al. 1989; Woods et al. 1993). Another study presenting word

stimuli to aphasic subjects who were instructed to listen to the words and occasionally had to repeat them, did not find N2 amplitude reduction (Rothenberger et al. 1982).

Although none of the present papers directly compared attended vs. unattended processing of tone stimuli in one aphasia group, we did not find significant reduction neither of passive discrimination activity of tonal duration differences (paper I) nor of active discrimination of tonal pitch difference (paper IV). However, the latter activity was significantly slowed leading to prolonged N2 and P300 latencies. These indirectly observed differences between passive and active tonal processing can not be easily interpreted and should not be overrated because two different parameters of tonal processing were investigated in two different groups.

For speech sounds, a comparative analysis of passive vs. active processing could be performed (cf. page 37); the results for this sample indicate clear electrophysiological differences between passive and active syllable discrimination in a time range of 175 to 325 ms after stimulus onset, i.e. at processing stages that underlie considerable top-down influence. While passive stimulus discrimination thus was largely unaffected by the brain damage, the aphasic subjects were able to compensate for their active discrimination deficit (as measured by ERPs) in the syllable discrimination task which was performed successfully. Thus, a compensational mechanism was effective in the rather easy task of syllable discrimination, but insufficient in language comprehension as demonstrated by the reduced clinical aphasia scores. The fact that many aphasic subjects complain about that they fatigue quickly and that they have difficulties communicating with more than one person simultaneously might be explained by this mechanism.

The results from the passive vs. active processing comparison should however be interpreted carefully because the findings regarding active discrimination processing were not reproduced in paper IV. Reduced active discrimination processing activity might be just one of several possible processing patterns in aphasia (cf. discussion on different compensational mechanisms, page 42).

The relation between impaired auditory and speech sound processing and overall language function

As mentioned earlier (page 17; see introduction of paper II for a more detailed discussion), the relation between deficient auditory and speech sound processing and language comprehension difficulties in aphasia remains unclear, although it has been studied rather intensively. An important finding of the present study is the observation of

processing changes in – with regard to the task – successful speech sound processing. This suggests that at least some aphasic subjects are able to compensate for processing disturbances in certain tasks. The possibility that these compensational mechanisms might work only in rather easy tasks, but not in more demanding real language settings, has been pointed out.

The present studies have detected some processing changes in aphasia compared to healthy controls which possibly can cause or contribute to impaired language comprehension which is observed in the vast majority of aphasic subjects: Reduced N1 amplitudes were observed in papers II (CVs) and IV (tones and CVs), while N2 amplitude in response to speech sounds was reduced in paper II and syllable-P300 amplitude almost significantly reduced in paper IV. Furthermore, target detection processing (P300) was found delayed in response to tones and speech sounds in paper IV. With regard to the impact of these processing changes on higher-level language comprehension, the strongest evidence in this present study comes from the observed correlation between N1 amplitude reduction and reduced clinical aphasia scores (paper II). Moderate correlations (r between 0.6 and 0.7) were observed at ipsilesional frontal and central sites underlining the importance of left fronto-central perceptual speech sound processing for auditory comprehension.

Are the observed processing disturbances specific for aphasia?

When processing changes are observed in aphasic subjects compared to healthy controls, they need not necessarily be caused by or directly linked to aphasia. As aphasia is defined by deficient language processing, differential responses to speech vs. non-speech stimuli – as observed for the N1 component – can indicate aphasia specificity. Additional indications can be derived from correlations between observed ERP changes and measures of aphasia severity which was found for speech sound elicited N1 amplitude. A third indication comes from different responses in aphasic subjects compared to other brain-damaged, but not aphasic, subjects. In this respect, paper IV showed significant syllable-N1 amplitude reduction only in the aphasia, but not in the non-aphasia group suggesting that N1 reduction in aphasia is not (only) a general effect of brain damage. Additional evidence for the specificity of N1 amplitude reduction in aphasia comes from the topographical pattern observed in paper IV, where compensational right hemisphere activity was significantly larger in response to syllables than to tones. To our knowledge, no other ERP studies have compared speech sound processing in aphasia vs. non-aphasic brain damaged subjects. A

study using word stimuli however found similar results: word-elicited N1 amplitude was reduced in the aphasia, but not in the right-hemisphere damaged group (Rothenberger et al. 1982).

Based on our results, it seems reasonable to conclude that brain injury in general entails some auditory processing changes, but that additional changes occur in aphasia that are specifically related to impaired language processing. These language-specific disturbances seem to appear already at early processing stages of perceptual integration of stimulus features.

Changes over time

Recent research indicates that the reconstitution of activation after brain injury can not implicitly be assumed to be a unidirectional increase after an acute reduction of activation caused by the brain damage (cf. page 23). In fact, transient hyperactivation has been observed in aphasia at two weeks (Saur et al. 2006) and three months (Ilvonen et al. 2003) post injury. In this respect, an interesting correlation in the aphasic subjects, none of them being examined before one month post-injury, was found in paper II: N1 amplitudes over ipsilesional frontal areas were smaller when more time had passed since brain injury. Lower amplitudes observed in those patients who were investigated at later stages are in agreement with a transient increase of activation that diminishes or ceases over time, especially considering the fact that there was no correlation between time passed since brain injury and aphasia severity.

In the longitudinal study (paper III), there were no significant amplitude changes between sessions and only minor clinical improvement was present. We did however register changes in hemispherical distribution of attended discrimination activity between three and seven months post injury which can be interpreted as the regression of temporary compensational increase of right hemisphere activation. A similar finding was reported in a recent fMRI-study that observed increased right hemisphere activation at twelve days post stroke that had normalized eleven months later (Saur et al. 2006).

We observed individual ERP patterns that illustrate the variation between subjects. This underlines the need for further research with larger and more homogeneous groups, and more comprehensive investigation of single cases.

Topographical changes

Several of the present results indicate compensational right hemisphere processing in aphasia: the left-lateralization of syllable-MMN observed in the healthy control group was not present in the aphasia group; rather, increased right frontal amplitudes were observed (paper I). N1 amplitude peaked over the right hemisphere in a severely aphasic group, while it was centralized in a moderate aphasic group and in healthy controls (paper II). This finding is in line with the traditional view that ipsilesional recovery patterns lead to better outcomes than mechanisms based on contralesional brain areas. Furthermore, a difference in hemispherical N1 distribution depending on stimulus type was found, with larger right hemisphere amplitude overweight for syllables than for tones (paper IV). For active stimulus discrimination and classification activity, a shift from a right- to a left-hemisphere maximum was observed between three and seven months post injury (paper III).

As mentioned above (cf. page 21), recent research has given more insight into plastic changes after brain injury. Although the understanding of these phenomena is very premature, there are indications that post injury plasticity is complex and influenced by a number of factors. Since language processing involves a large number of brain areas and neural networks, it seems possible that there also is a number of 'plasticities', i.e. that these different networks can behave differently in response to brain damage and might be influenced in different manners by factors as post-injury time, etiology, therapy etc. In this regard, differences in the recovery of frequency discrimination MMN vs. pitch discrimination MMN have been reported (Ilvonen et al. 2003).

On the background of the possible existence of several plasticity patterns, it has been suggested with regard to the ipsi- vs. contralesional hemisphere debate that compensational mechanisms in the premorbid non-dominant hemisphere are more important for language comprehension than production (Demonet et al. 2005; Marsh & Hillis 2006). The present results support this notion in that compensational right hemisphere activity in speech sound comprehension processing was observed. This is also emphasized by our results regarding different topographic patterns for tonal vs. speech sound stimuli in aphasia. Additionally, the present findings are in line with the suggestion of transient plastic changes, both regarding hyperactivation and hemispherical change.

A nose-reference – in opposition to mastoid reference – was chosen for our investigations because we were particularly interested in activation changes in temporal regions. However, this strategy led to noteworthy results only in paper I. Here, both ipsi- and contralateral mastoid MMN amplitudes were reduced in the aphasia group compared to the controls, but

these differences did not reach significance although they were present in response to both stimulus types. However, a significant group effect regarding hemisphere distribution of the mastoid tone-MMN was found: A lateralization to the left side was present in the controls, but not in the aphasia group. The speech sound MMN did not show any mastoid lateralization, neither in the controls nor the aphasics, the latter group showing a bilateral attenuation (though this attenuation was somewhat larger in the left hemisphere).

Although – as mentioned above (cf. page 44) – the gradient of more posterior processing of speech sounds compared to tones grossly was preserved in the aphasia groups investigated, more anterior processing of speech sounds in aphasia compared to controls was observed for MMN (paper I), N1 (paper II, moderate aphasia group), and P3 (paper II). As all these components have several generators including frontal ones, these results can be interpreted as larger involvement of frontal processing in aphasia. This might be an expression of damage-related mechanisms where reduced primary processing in temporal regions is compensated for by the allocation of attention-dependant frontal processing resources.

Clinical use of ERPs in aphasia rehabilitation

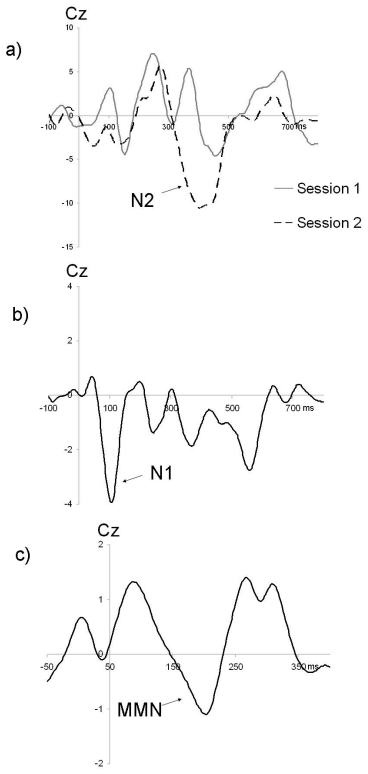
One especially interesting clinical use of ERPs in aphasia diagnosis and treatment would be the measurement of language comprehension function. Patients' comprehension abilities are not always easy to assess and an additional method beyond clinical tests is needed. Moreover, this field of use would be interesting for other patient groups than aphasic subjects, e.g. patients with severe traumatic brain injury or locked-in syndrome. From our results, the N1 component seems most promising in this respect: Its amplitude was the only parameter that correlated with results from clinical aphasia assessment and our findings regarding tone- vs. syllable-N1 and topographical distribution changes indicate some form of specificity for language-related processing.

As N1 is an early, so-called exogenous, component, it could be argued that N1 reflects pre-linguistic processing stages which hardly can be critical for language comprehension. Recent studies have shown that phonological features of speech sounds modulate the magnetic counterpart of N1, the M100: For example, phonological features of vowels influence peak latency of the M100 waveform and spatial location of the M100 dipole source (e.g. Obleser, Lahiri & Eulitz 2004), and consonants differing in voice onset time elicit different M100 responses (Frye, Fisher, Coty, Zarella, Liederman & Halgren 2007). Furthermore, differences in the processing of an acoustic stimulus depending on whether it

was delivered in a language context or not, have been observed already at 100 to 150 ms post stimulus onset (Shtyrov et al. 2005). Processing deficits at these early stages, reflected by disturbances in the EEG recorded N1 component, might thus play a role for auditory comprehension impairments in aphasia. On the other hand, our results regarding the correlation between N1 amplitude reduction and auditory comprehension impairment could primarily be a result of lesion size and thus brain damage severity: the larger and graver the lesion, the more severe the aphasic impairment and the larger the N1 amplitude reduction. Further research on the N1-component is needed to investigate its possible usefulness in clinical settings.

Of special interest is the use of ERPs as a prognostic tool on the basis of an assumption that electrophysiological parameters of successful recovery can be detected before they are expressed through behavioral responses. In this respect, an interesting observation was made in our longitudinal study (paper III): Patient 5 was the only subject in that study who was unable to perform the syllable discrimination task in the first session. She improved during rehabilitation and performed the task correctly at retest. This behavior is reflected by the difference waveforms from the attended discrimination paradigm: while the waveform from the first session does not show an N2, this component can clearly be observed in the second waveform (figure 4a); the N2 latency is however prolonged, which corresponds with the patient's long reaction time of 970 ms. Interestingly, ERPs from the first session reveal that although active discrimination was impossible for her at this point of time, brain activity related to primary stimulus feature analysis and automatic and pre-conscious syllable discrimination were present also in the first session as reflected by the presence of both N1 and MMN component (figure 4b and c).

Figure 4



Waveforms of patient 5 from paper III, recorded at two (session 1) and nine (session 2) months post injury: a) subtraction waveform from active syllable discrimination paradigm, b) waveform elicited by standard syllable in active syllable discrimination paradigm, c) subtraction waveform from passive syllable discrimination paradigm.

While the N2 potential is observed first at session 2, N1 and MMN are present already at session 1.

This finding underlines the method's ability to evaluate cognitive processing in single patients and illustrates its prognostic potential. Investigating a large number of brain-injured patients, Kotchoubey et al. showed that the presence of early, automatic components usually is a prerequisite for the presence of later components reflecting cognitive activity (Kotchoubey et al. 2005). It can be speculated that the presence of these pre-conscious, syllable-elicited components also is a positive prognostic factor with regard to recovery of an active speech sound discrimination function. Studies on patients with severe traumatic

brain injury have shown that ERPs obtained at early stages predict outcome (Fischer, Luaute, Adeleine & Morlet 2004). Additionally, the validity of ERP assessment independent of behavioral responses (D'Arcy et al. 2003) as well as test-retest reliability has been shown (MMN: Kujala, Kallio, Tervaniemi & Naatanen 2001; Pekkonen, Rinne & Näätänen 1995; Sinkkonen & Tervaniemi 2000; Tervaniemi et al. 1999; N1: Pekkonen et al. 1995; Virtanen, Ahveninen, Ilmoniemi, Näätänen & Pekkonen 1998).

On the other hand, findings of normal ERP responses together with impaired behavior or of ERP changes together with successful task performance as for the N2-component in paper II, somewhat complicate the picture. A strict correlation between cognitive abilities and the presence and maybe size of a component is preferable when one aims to measure language comprehension with ERPs. On the contrary, the presence of certain ERP findings preceding the recovery of behavioral responses is the target when prognostic use is focused upon. More research – not at least through thorough descriptions of single cases – is needed to enlighten the complex relationship between electrophysiological correlates and behavior.

Methodological issues

Some of the methodological weaknesses of the present study concern patient selection. The participating patients are not representative for the aphasic population in general. This is mainly due to the patient specter at Sunnaas Rehabilitation Hospital where especially rather young and more severely impaired patients are treated. The results can not be generalized without reservation for aphasia in general, but they still give interesting insights in some mechanisms that exist in aphasia.

Furthermore, the patient groups were rather heterogeneous with regard to several variables, especially regarding lesion site / size, etiology, and time post injury, but also regarding age and aphasia type. Although the total patient number was rather large compared to the majority of existing ERP studies of aphasia, this heterogeneity in combination with limited group sizes can lead to an overrating of results that are not especially relevant for the aphasia population in general. Additionally, important findings might remain undiscovered because they appear only in subgroups and thus are blurred in the averaging process. However – with regard to clinical use of ERPs in aphasia – those effects are most interesting which are present regardless of variances in other parameters as etiology, lesion site, time post injury etc.

The variability of lesion site and size is thus one important problem of this study. A related issue is the fact that the study protocol did not include structural neuroimaging, but

that lesion data were retrieved only from the patient's clinical charts and imaging results. It is thus difficult to relate the electrophysiological results to brain areas. Although the role of different brain areas to auditory processing deficits in aphasia was not a primary aim of this study, more detailed lesion data could have contributed to a better understanding of the present results. Furthermore, some results, e.g. the observed differences between the two patient groups in paper IV, might have been influenced by differences in lesion size and site. Whether this is the case is difficult to assess based on the lesion data available. Future studies should preferably include CT / MR scans as part of the study protocol allowing more detailed descriptions and investigations of lesion site and size.

In light of recent studies that indicate complex dynamics of brain activation after brain injury (cf. page 23), the present variation in post-injury time is another important limitation. In addition, in particular with respect to the fact that aphasia recovery to its largest parts occurs during the first three months post injury (Laska et al. 2001; Reinvang 1985a), investigations more close to the time point of injury should be performed, especially with regard to longitudinal studies.

Results regarding the question of speech vs. non-speech processing should be considered cautiously, because the stimuli used did not only differ in the speech / non-speech parameter, but also with regard to stimulus length, sound pressure level etc. Observed differences might thus have been caused by other parameters than the speech vs. non-speech contrast. As mentioned above (cf. page 43), the speech vs. non-speech discrimination is not straightforward and there are indications that also parameters that are not innate to the stimulus determine whether a stimulus is processed as a speech or a non-speech stimulus (cf. Shtyrov et al. 2005). Nonetheless, a reduction of deviating parameters between stimulus types does allow more substantiated conclusions. In addition, paradigms that are contrasted in order to compare different brain processes should preferably have similar contrasting features between standard and deviant / target stimuli, both with regard to what parameter is contrasted and the magnitude of the contrast.

In addition, some general limitations regarding the ERPs-method have to be considered. Reduced amplitudes measured by electrodes in a certain location have a complex relationship to underlying brain activity. Lesion effects as atrophy, gliosis, or edema can influence the registration of activity from nearby generators. In addition, amplitude changes might be due to effects in remote brain areas (diaschisis (von Monakov 1914)). In general, ERPs have its limitations in the study of topographical distribution of activity and is in this regard inferior to other neuroimaging methods as MEG, fMRI or PET.

Finally, one has to be cautious when comparing the results regarding different processing stages in order to detect which of them are especially impaired in aphasia. It has to be taken into account that both significant differences and correlations with clinical aphasia measures are easier obtained in earlier than in later ERP components due to the fact that inter-individual variation is smaller in earlier components. Later components are more vulnerable for this effect, i.e. one might observe mean amplitude reductions that are caused rather by inter-individual latency differences than by consistent individual amplitude attenuations.

A factor that potentially could have influenced the present results, but that was not controlled in the study design, is depression. Post-stroke depression has been shown to affect long-latency ERPs, for example has prolonged P300 latency been found to be related to post-stroke depression (Korpelainen et al. 2000). Although an assessment of the prevalence of depression was not part of any of the papers, post-hoc review of the patient's medical and psychological charts and of their use of anti-depressive medication did not reveal major differences between the four patient groups participating in our two studies, which makes it unlikely that depression is responsible for the observed P300 latency increase or the diverging results.

Conclusions and future research

Based on the present results, it is suggested that auditory and speech sound processing in aphasia is disturbed in several processing stages and that already early steps of stimulus processing might contribute to language comprehension impairment in aphasia. The possible direct relation of these early changes at about 100 ms post stimulus to speech sound processing deficits should be confirmed by further studies.

The early processing disturbances did not prevent the aphasic subjects from successfully discriminating syllables. Two different patterns were observed in later processing stages: reduced level of activity on the one hand and delayed activity on the other. This led to the suggestion that different compensational mechanisms for the early processing differences exist. Since this suggestion is derived from diverging results in two patient groups who were investigated with a new, unexplored paradigm, further investigations using this or similar paradigms should be conducted to verify the results and seek for parameters that define possible subgroups.

In the recovery from aphasia, the relationship between clinical improvement as measured by behavioral assessment and processing changes as registered with ERPs seems to be a complex one. Future research should address this question. A more sophisticated understanding of this complex relationship will allow us to clarify when and how ERPs can be used in clinical medicine and in rehabilitation. In this present study, a correlation between N1 amplitude and auditory comprehension abilities was observed; it should be investigated more closely.

Some of the present results are consistent with increased right hemisphere involvement in aphasic speech sound processing, especially in severe aphasia. In addition, inter-individual differences of topographical distribution were observed. As discussed earlier, recent research has provided new insight into how language works in the brain and suggests that language processing is more complex and sophisticated as earlier assumed. The suggestion of bi-laterality of the acoustic / language processing network and the disclosure of two pathways within the left hemisphere are examples in this regard. For example, no simple answer seems to exist to the old and much debated question of whether it is the left or the right hemisphere that is essential in aphasia recovery. Instead, there might be a number of answers that address different aspects of language and of cognitive processing and that depend on several parameters which are exposed to large variations.

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